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THE SABLE VARIETIES OF MICE

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THE variations in darkness of certain forms of fancy mice have called forth different interpretations from the various investigators who have studied them. The present report is intended as a contribution of experimental data, treating these differences as graded variations.

The varieties of mice most commonly exhibiting differences in darkness comprise those races known as sables. Such mice are distinguished by a yellow belly and a back of some shade of black or brown with which yellow may or may not be mixed. They were first reported by Bateson in 1903 but Miss Durham (1911) was the first to breed them experimentally and to catalog the variations within the sable race. Little (1913) classed sables as yellows with varying amounts of dark pigment in the hairs on their dorsal and lateral surfaces. Dunn (1916) offered the explanation that all sable varieties differed from ordinary yellow by a factor or factors determining the quantitative increase of dark pigments, so that sables formed a continuous series of increasing dark dorsal pigmentation from clear yellow to black-and-tan in which the back was intense black while the yellow pigmentation was exhibited only on the belly. Onslow (1917) was "led to look upon sable as a pattern factor which could give a yellow belly to a mouse of any color," but he did not publish the experimental evidence upon which his conclusions were based. He criticized Dunn for further involving the nomenclature of the sables through the use of the names "black-and-tan," "brown and tan," "black sables," and "brown sables," to designate the members of the sable series.

The use of the above term is, I believe, justified because black-and-tan is recognized by the English fanciers as distinctly different from ordinary sable, and because none of the sables described by Miss Durham behaved as did the mice used in my experiments. Miss Durham described "black, blue, chocolate and silver fawn mice which differ only from the ordinary forms by having yellow bellies," but they subsequently always moulted into ordinary sables which have a "dark black or brown streak down the middle of the dorsal region while the rest of the mouse is yellow." Black-and-tan however does not moult to ordinary sable. Even at the age of twenty months black-and-tan is entirely black except for the yellow belly and yellow ticking on flanks and muzzle. Since these mice were different from ordinary sables, they were given a name to indicate the difference. Moreover when they were crossed with various non-black-and-tan varieties there were produced in the second generation mice resembling the black-and-tan parent, others intermediate between black-and-tan and yellow, and conforming to Miss Durham's description of sable. The latter were called black sable or brown sable to indicate the color of their non-yellow pigment. I am in sympathy with Onslow's desire to prevent a duplication of terms but I believe that the names employed are required by the presence of types which differ both genetically and somatically.

Sooty yellows may likewise be included in the sable series since these mice appear when black-and-tans or sables are crossed with non-sable varieties. Sooties can not be distinguished simply as yellows which are heterozygous for black, for yellow mice which carry black may show no trace of sootiness. Factors additional to the black gamete are involved in the production of sooties and these factors are present not only in the sooties but in the blacks which they produce. Little (1916) used blacks derived from sooties in crosses with wild agouti and obtained agoutis which were much darker dorsally than any wild agoutis. I have obtained similar results from such crosses. Certain blacks with which yellows have been crossed to produce sooties evidently carry some of the factors for darkness which appear in greater concentration in sables and black-and-tan as well as in the blacks derived from these varieties. Sooty, then, appears to be a lower stage of sable in the more complete restriction of non-yellow pigments from the hair.

In addition to the varieties treated above it is necessary to speak of light bellied mice which can not be included in the sable series. I refer to the light-bellied agouti variants reported by Cuénot and Morgan. These variations have been shown to belong to a series of multiple allelomorphs in which the other members are ordinary agouti, yellow, and non-agouti. The light-bellied agouti also arose spontaneously in Little's 1916 crosses between gray-bellied agouti and dilute brown. Such light-bellied agoutis bred true and when crossed with a non-agouti variety they produced in F_2 only light-bellied agoutis and normal non-agoutis. This result contrasts strongly with the result of a cross of black-and-tan with wild agouti which produces only sables and gray-bellied agoutis in F_1, while in F_2 there result yellows, sooties, sables, black-and-tans, agoutis and darkened agoutis. The difference is readily seen to be due to the yellow gamete of the sable series.

To explain the results of the genetic behavior of sables one is led to review the origin of the varieties concerned. The wild house mouse is undoubtedly the ancestral type from which all varieties of fancy mice have descended. Its pelage contains the three fundamental pigments of mice: yellow, black and brown, formed in the mosaic known as the agouti pattern by the presence of a specific gene "A." Each pigment is likewise determined by a gene, Y for yellow, B for black, b for brown (absence of black) and by loss of one or more of these genes, or by the gain of other genes determining the distribution of the pigments present, the whole array of fancy varieties has resulted.

Yellow was shown by Cuénot to be due to a change in the gene "A," resulting in the presence of a restrictive factor which limits the distribution and amount of black and brown pigment, the eyes alone being dark pigmented while black or brown pigments are present in the hair and skin in such small amounts as to leave the pelage clear yellow. All three fundamental pigments are present in yellow and it is essentially an agouti in which the dark pigments are quantitatively restricted and reduced. This gene acts as the dominant allelomorph of agouti, light-bellied agouti, and non-agouti. Black mice, on the other hand, represent no quantitative reduction in amount of pigment but only the absence of the genes for yellow and agouti. The sables contain a gene allelomorphic to agouti and non-agouti. The evidence shows that this gene is common to yellow, sooty, sable and black-and-tan mice. This gene is a lethal. When it is present in both gametes uniting to form a zygote it causes the death of the zygote. This lethal gene (yellow) might conceivably assume several forms and cause the differences noted among the sable varieties. If such were the case, yellow and sable varieties would be members of a series of multiple allelomorphs of a single gene. Such series have been demonstrated in the gene for white eye in Drosophila by Morgan and his co-workers; in the color gene in the guinea pig by Wright (1915); and in the agouti gene in the mouse itself as quoted previously. But if the black-and-tan mouse or a sooty were due simply to a different form of the yellow gene the difference of their black recessives from ordinary blacks would still remain to be explained. Moreover yellow and the members of the sable series are more closely related to each other than as mere members of a multiple allelomorphic series. They do contain an identical gene, and unlike multiple allelomorphs can be changed one into the other more or less completely. Their difference rather inheres in their possession of modifying genes determining the quantitative increase of black or brown pigments not only in connection with the yellow gene itself but in connection with the genes for black, brown and agouti.

Such modifying genes can not be merely changes in a distributive gene such as agouti or the gene for restriction which causes yellow, for their presence has been demonstrated in non-agouti, non-yellow animals. They must rather be related to the formative genes for black and brown pigment, so that the number of black and brown pigment granules is increased in proportion to the number of modifying genes present. I have examined microscopically hairs from the mid-dorsal region of a black-sable mouse which was intermediate in color between black-and-tan and yellow, from pure black-and-tan and from clear yellow mice of the same age. The cause of the difference among the hair colors of these three forms was clearly the varying number of black pigment granules. In the yellow hair the dark granules were extremely rare and poorly defined, appearing in many cases as partially mixed with the diffuse yellow ground color. In the sable hair the black granules were more numerous, occurring singly in the distal third of the shaft, while in the proximal two thirds the concentration was greater. Here the granules were large, one granule usually extending across the medullary space. In some cases two granules appeared side by side, and in rare instances I noted rows of three across the hair. In the hairs from the black-and-tan the concentration of granules was three to ten times as great as in the sable hair; the whole shaft was filled with closely packed small black granules. One row was rare; two was common; the rule was three or four rows, while I sometimes found rows of six small granules packed closely into the width of the hair.

If, as I have stated, there exist in mice genes determining the quantitative increase of dark pigments, it should be possible by experiment to test their existence and to determine whether they are Mendelian in behavior or not and whether they are simple or multiple. The data which follows is submitted as a test of the above questions.

According to the provisional hypothesis, black-and-tan being the darkest member of the series should genetically contain the greatest number of modifying genes. The presence of such genes should become apparent if black-and-tan were crossed with a race containing the dark pigments but lacking entirely any of the modifying genes. These conditions were satisfied only by pure wild house mice, caught at a distance to insure against any contamination from crossing with fancy varieties. These wild mice were regarded as lacking the darkeners; black-and-tan as containing the maximum concentration of darkeners; and after some preliminary experimentation it was decided that si ess could be distinguished of which th ded as grade 1 and black-and-tan as gra not represent all the grades that actually variation from one to six was practically continuous but such arbitrary points had to be fixed for convenience in observation and record. These grades were standardized by means of type skins for each grade with which each mouse was compared at the age of three weeks and at later intervals throughout life.

The results of crossing black-and-tan with wild agouti are seen in Table I and Fig. 1. The first generation consisted of two classes of young, darkened yellows and darkened agoutis. The mode of the F_1 yellows was at grade 3, and their mean grade was 3.3 both practically midway between the parent grades. The mode of the F_1 agoutis was at 2 and their mean grade was 2.8 showing that although they represented a blend between the parental types the agouti pattern affords a less favorable background for the development of darkness than does yellow.

Two F_2 generations were raised, one by inbreeding the F_1 yellows, the other by inbreeding the F_1 agoutis. The distribution of F_2 yellows shows the increased variability which we have come to expect from such blending characters as size and other quantitative measurements. Evidence of segregation of parental characters appears from the presence of a large number of grade 1 (yellows) and the separation of this class from the other large class (grades 3 and 4) by a small class (grade 2). Segregation of darkness may also be inferred from the large class at grade 5 which contained relatively few individuals in F_1. The mean grade of F_2 is 3.0 indicating that the average darkness has not changed while the distribution has changed considerably. The same is true in a lesser degree of the F_1 agoutis resulting from the inbred F_1 yellows and of the progeny of the inbred F_1 agoutis. In the latter class strong evidence of the segregation of the undarkened wild is apparent from the large size of grade 1

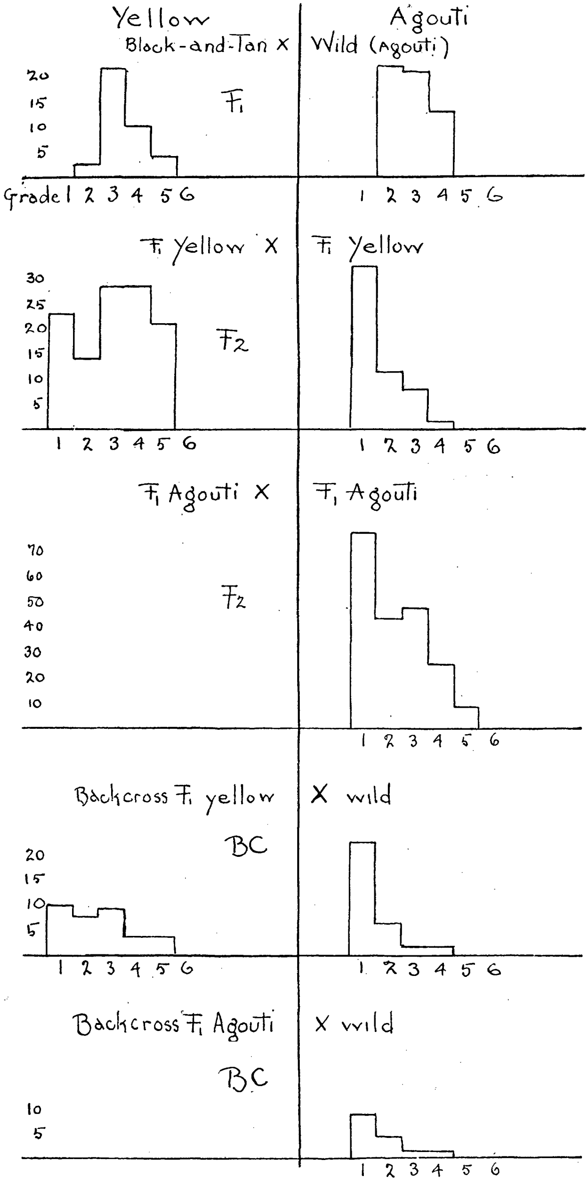

FIG. 1. Crosses of Black-and-Tan with Wild.

TABLE I

CROSSES OF BLACK-AND-TAN WITH WILD AGOUTI

Cross Number	Parents by Generation and Grade	Yellow Young by Grades						Agouti Young by Grades						Total Young	Total Yellow	Yotal Agouti	Total Black	Mean Yellow	Mean Agouti
		1	2	3	4	5	6	1	2	3	4	5	6						
		Yellow	Sooty	Sable	Dk. Sable	Blk-Tan.Lt.	Blk.-Tan												
I.	Blk.-Tan (6) × Wild Agouti (1)		2	21	10	4			23	22	13			95	37	58		3.43	2.83
II. . . .	F_1Agouti (2, 3, 4) × Fi Ag.							78	43	46	25	9		211			57		2.22
III. . .	F_1 Agouti (3) × Wild (1)							8	4	1	1			14		14			1.64
IV . . .	F_1Sable (3. 4) × F_1 Sable (3, 4)	23	14	27	27	21		33	12	8	1			166	112	54		3.08	1.58
V	F_1 Sable (3, 4) × Wild	10	8	9	4	4		23	6	2	2			68	35	33		2.54	1.49
VI . . .	F_2 Blk. and Tan (light) (5) × Wild			7	1			4						8	8	4		3.12	1.00
VII . .	F_2 Dk. Sable (4) × Wild	3	3	6	3			28	2					45	15	30		2.60	1.07
VIII. .	F_2 Sable (3) × Wild	3	2	2				8						15	7	8		1.86	1.00
IX . . .	F_2 Sooty (2) × Wild	4	3					8						15	7	8		1.43	1.00
X. . . .	F_2 Yellow (1) × Wild	8						10						18	8	10		1.00	1.00

(wild). The average grade of these F_2 agoutis is 2.2, slightly lower than the F_1 grade while two new grades have been added to the distribution, grade 1 (wild) and grade 5 (very dark agouti). A few back crosses were made of F_1 agoutis with wild, and of F_1 yellows with wild. These showed likewise segregation of undarkened yellows and undarkened agoutis and lower mean grades than F_1—2.5 for yellows and 1.5 for agoutis.

The results thus far had established the presence of a factor or factors for darkness, the formation of intermediates in F_1 when crossed with animals lacking it, and the incomplete segregation of parental types in F_2. They had not answered our questions regarding Mendelian behavior or number of factors involved. This failure may have been due to incorrect observation, to the failure of the grading scale to distinguish between the types produced or to the actual non-appearance of the types expected. By constant application and regrading it was believed that the error from the first two reasons was low. To consider the third, one must recall what is known of the origin of the black-and-tan variety. It has been for some years a standard breed of the English fancy, built up probably through the constant selection by breeders of the points it now possesses—clear yellow belly and intensely black back with a sheen not duplicated in any other variety or in the hybrids of black-and-tans with other varieties. Since the variety breeds quite true these points must be heritable, and one can hardly expect to extract the pure type of black-and-tan from a cross with wild without practising upon the segregates a selection similar to that which perfected the variety. This involves the supposition that the factors causing the darkness of the black-and-tan are very numerous and extremely small in individual effect.

The F_2 darkened agoutis were chosen as the starting point of a selection for darkness which lasted through several generations. These agoutis were easier to grade because they were non-yellow; their litters were larger for the same reason, and it was also desired to know whether the fact that black-and-tans were always heterozygous for black was a cause of their darkness. The results of mating together dark agoutis of various grades is shown in Table II and Fig. 2.

TABLE II

CROSSES OF DARK AGOUTIS INTER-SE

Parents	Grade Distribution of Young									
	1	2	3	4	5	5.5	6	Total Ag.	Mean Grade	Blk.
XI. 1 × 1	32							33	1.00	1
XII. 2 × 2	11	21						33	1.60	1
XIII. 4 × 2	11	18	6	3				38	2.02	2
XIV. 4 × 3			6	5				11	3.45	1
XV. 4 × 4			7	6				13	3.46	0
XVI. 5 × 4		1	10	8	16	5	4	51	3.83	13
XVII. 5 × 5		3	17	33	28	18	6	105	4.38	18
XVIII. 6 × 4		1	5	19	19	8	13	68	4.66	2
XIX. 5.5 × 5.5				4	4	8	5	21	5.23	7
XX. 6 × 5			6	20	41	47	21	135	5.09	30
XXI. 6 × 6				6	16	23	27	72	5.45	18
XXII. 6 × 1 (wild).....	13	26	19	8	6			72	2.55	0
I. Blk.-tan × wild..		23	22	13				58	2.83	0

The table shows plainly that the variation in darkness is practically continuous. Animals of grade 1 proved to be pure wild segregates entirely lacking the darkeners. Grades 2, 3 and 4 contained the darkener but never produced by recombination any animals darker than their own grade. Grades 5, 5.5 and 6 produced grades both darker and lighter than their own, proving them to be heterozygous in the modifiers. None of these darkest grades proved to be pure dark segregates. Even grade 6 which was entirely black with a gray belly and quite comparable in darkness to black-and-tan produced animals of grade 1 (light segregates) when crossed with wild agouti. These grade 1 agoutis were tested and found to lack any modifiers for darkness. Therefore grade 6 in darkness was not homozygous as regards the darkening modifiers.

The supposition that the darkness of the dark agoutis might be due simply to their being heterozygous for black was disposed of by the results of the dark agouti crosses, for of eighteen F_2 dark agoutis thoroughly tested, twelve were heterozygous for black and six were homozygous agoutis. In subsequent generations selection was in the direction of darkness. That this was not accompanied by selection of heterozygotes is shown by the figures for dark agoutis of F_3, F_4 and F_5 which were tested. In generations F_3 and F_4 there were twenty agoutis heterozygous for black to 8 homozygous agoutis; in F_5 four heterozygotes to three homozygotes, and the homozygotes comprised some of the darkest mice produced. Another explanation for the darkness of the agoutis must be invoked and the data indicate that the only alternative is the ac-

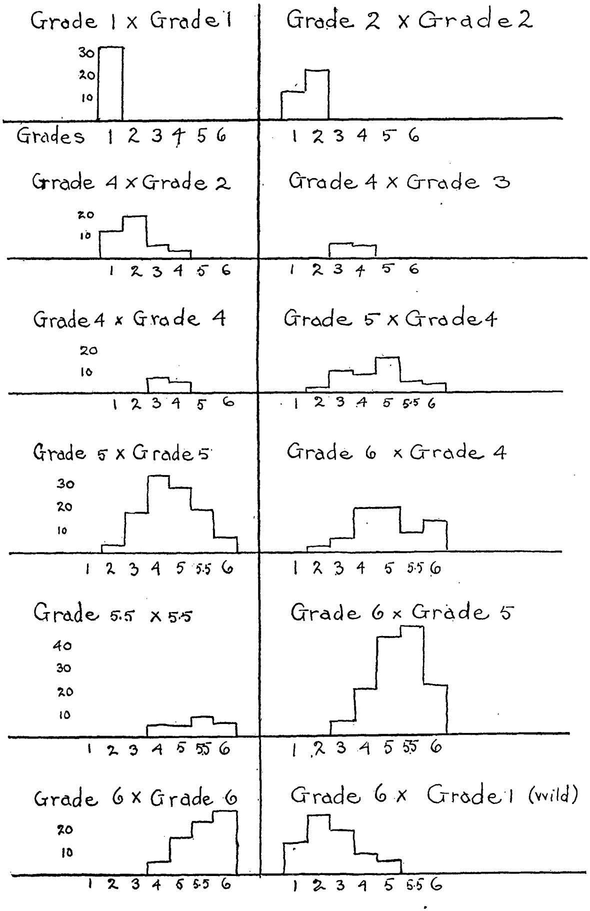

FIG. 2. Crosses of Dark Agouti Inter-Se.

quisition by the dark agoutis of the peculiar and puzzling darkness from the black-and-tan race.[1]

Up to his point the data has involved crosses of darkness with its absence—and crosses of dark animals of various grades inter se. Multiple factors appear to be involved and yet no evidence of Mendelian behavior has been adduced except the segregation of lack of darkness without accompanying segregation of darkness.

Many additional crosses have been made in which the darkeners from the sable series have transferred into other varieties with results similar to those outlined above. The most extensive of these secondary experiments involved crosses of black-and-tan with brown (chocolate) mice to test the black-and-tan (yellow) gamete and to separate if possible the darkening modifiers (see Table III and Fig. 3). This cross brought about the union in the first generation of gametes with full darkness (black-and-tan) with a uniform set of gametes from the brown race all of which supposedly lacked the darkener. The first generation from this cross showed, as was expected, the dominance of black, all young being black pigmented. Approximately one half were self black which on being tested proved to be heterozygous for brown. The other half were a lightened black-and-tan (Table III, cross 23) with some variation but none were as black as pure black-and-tan. The number of dark pigment granules in the dorsal hairs was reduced and the yellow pigment substratum was thereby allowed to show at bases and tips of hairs especially in the older animals. From these light black-and-tans was bred an F_2 generation (cross 26) consisting of mice with black pigment and mice with brown pigment in approximately the ratio 3:1. Of the blacks about one third were self black; the others were yellows, sooties and black sables with varying amounts of black in the fur, much like the F_2 array in the black-and-tan × wild agouti cross. In this F_2 distribution were seen, besides all grades of intermediates, segregates of both sorts, viz., yellows of grade 1 and black-and-tans of grade 6, although the latter did not retain their darkness throughout life and when bred proved not to be pure segregates. The F_2 mice with brown pigment were similarly divided into yellows and brown sables with varying amounts of brown in the fur and self brown in the ratio 2:1. Of the yellow-browns some were evidently counterparts of black-and-tan with the black pigment replaced by brown. To these the name brown-and-tan was given; the other yellow-browns paralleled the yellow-black series although the lower and intermediate grades were less well represented, due perhaps to the difficulty of distinguishing between yellows with considerable brown pigment and yellows with smaller amounts of black pigment. Breeding tests were used in doubtful cases.

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[1] Morgan in 1914 reported the appearance in his experiments of mice to which he gave the name "new gray," which were noted first in the offspring of a pair of cinnamon mice. They "looked like chocolates, but . . . showed on later inspection distinctly ticked hair. One of these new grays bred to black (heterozygous) gave some chocolates, black, new grays, and one very dark, almost black, mouse." The above descriptions apply quite accurately to cinnamon and agouti mice which I have raised from crosses with one of the sable series and I have little doubt that the darkness of Morgan's new grays was derived originally from some mouse carrying the "darkener."

TABLE III

CROSSES OF BLACK-AND-TAN WITH BROWN

Cross No.	Parents	Yellow and Black Young										Yellow and Brown Young								
		1	2	3	4	5	5.5	6	Mean	Blk.	Tot.	1	2	3	4	5	6	Mean	Brown	Tot.
23	Blk.-tan × Br.....				4	17	6		4.96	19	46									
24	F_1BT × F_1BT.....	2	1	2	3	12	26	14	5.15	26	86	0	2	1	1	8	10	5.05	12	34
25	F_1BT × brown....	5	3	11	2	4	2		3.00	30	57	9	2	7	0	10		3.00	26	54
26	BT × Br. and tan 6				1	1	0	2		3	7									
27	F_1BT × F_1BT from cross 26.......				1	2	5	17	5.74	7	32					3	3		5	11

The F_1 light black-and-tans, when backcrossed to browns (Table III, cross 24), gave equal numbers of all four sorts, viz., yellow-blacks, self blacks, yellow-browns and self browns. The mode of these yellow-blacks was in the middle class (grade 3) in contrast with the mode at 5.5 in the straight F_2.

These crosses of black-and-tan with brown show the independence of the darkeners from black pigment for in these experiments the modifiers have been detached from the black pigment on which they operate in the pure black-and-tan and transferred to brown pigmented yellows where their action is similar. Their independence of yellow was illustrated by their action on agouti mice.

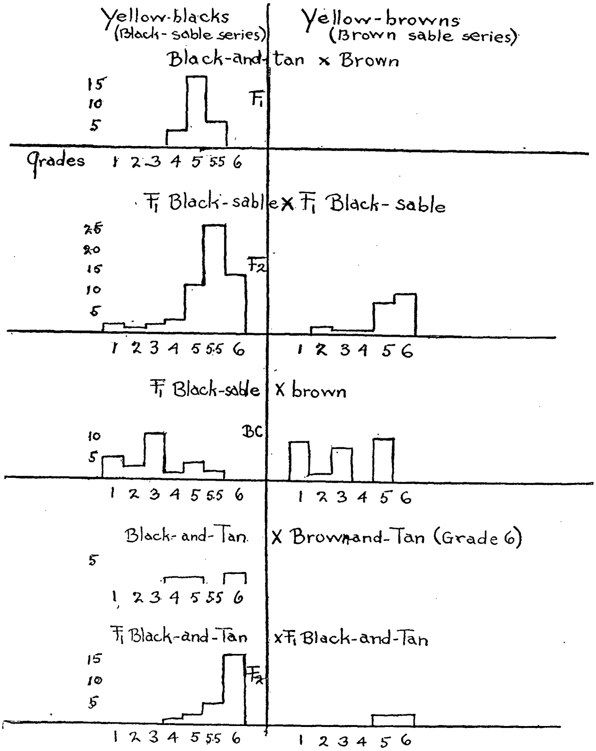

Fig. 3. Crosses of Black-and-Tan with Brown, Yellow Young by Grades.

The intermediate nature of F_1 in the black-and-tan × brown cross and subsequent segregation of dark and undarkened forms is not as clear as in the agouti crosses, for it is probable that the brown parent contributed factors comparable to the darkeners which have acted to make both F_1 and F_2 darker than if the darkening factors had come only from the black-and-tan parent. The browns used were derived from a yellow variety known as red. Both the reds and their brown recessives are more intensely colored than any other yellows or browns, and in fact have given evidence in later experiments of differing from ordinary varieties by intensity factors similar to the darkening factors of black-and-tan.

The results throughout indicate that we are dealing here with genetic factors similar to those which have produced such quantitative differences as size in the races of rabbits studied by Punnett. The results obtained from crossing large and small races of rabbits agree in the production in F_1 of animals genetically intermediate between the parent races, and in the evidence of subsequent segregation of the smaller size without segregation of the larger. The same phenomenon appears in the present study for light segregates have appeared but never the dark. Placing the causes of darkness in mice in the same category with the causes of size differences, which have not yet been made clear, is an admission of the unsuitableness of the material rather than of the insoluble nature of the problem. Either the best material for the investigation of such grade variations has not yet been found or else the technique of observation and measurement of such genetic differences as distinguished from non-heritable differences has not yet been evolved. The correct interpretation of such differences must await an investigation combining an optimum of material and method.

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